

Application No.: 10/614,648
Filing Date: July 7, 2003

REMARKS

Claims 93-125 are currently pending. Applicants have amended Claims 93, 104, 105, 113, 115, 116, 119, 120, 121, 122, and 124. Applicants have amended Claims 93, 104, and 115 to specify that the unprocessed adipose tissue comprises “intact, non-disaggregated tissue fragments.” Applicants have also amended Claim 115 to substantially incorporate all of the limitations present in allowed Claim 93 of U.S. Patent Application No. 10/614,644. The amendments add no new matter and are fully supported by the specification and claims as originally filed. Support for the amendments can be found, for example, on page 40, lines 26-28, and elsewhere throughout the specification.

Claims 93-125 are pending and stand rejected by the Examiner. Applicants respond below to the rejections set forth in the Office Action mailed October 10, 2007. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 93-125 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over U.S. Patent No. 6,777,231 to Katz et al. (“Katz”) or over U.S. Patent No. 6,200,606 to Peterson et al. (“Peterson”). The Examiner states that both Katz and Peterson teach compositions comprising adipose-derived stem cells in a complex mixture and substantially free of other cells and tissues. According to the Examiner, the only difference between Applicants’ claimed compositions and the compositions taught by Katz and Peterson is the concentration of the cells and tissues contained therein, and, absent evidence that the concentration of the adipose-derived stem cells is critical, the alleged differences do not render the claims patentable over the cited art. Applicants respectfully traverse.

Briefly, as set forth below, Applicants maintain that Katz and Peterson fail to support a *prima facie* case of obviousness under 35 U.S.C. 103(a) because they fail to teach each and every element of Applicants’ claimed compositions. Furthermore, the references teach away from Applicants’ invention. In addition, Applicants provide herewith evidence that Applicants’ claimed compositions provide unexpected benefits and satisfy a long-felt unmet need in the field.

Claims 93-125 are not *prima facie* obvious over Katz and Peterson

The Katz and Peterson references, alone and in combination do not teach or suggest all of Applicants’ present claim limitations. Neither the Katz nor the Peterson compositions contain

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“unprocessed adipose tissue comprising intact, non-disaggregated tissue fragments”, as recited in Applicants’ claims. Additionally, Applicants’ claims are directed to a composition that comprises a “mixture of unprocessed adipose tissue comprising intact, non disaggregated tissue fragments. . .and a concentrated [] population [of] adipose-derived stem cells,” and the Katz and Peterson references do not teach or suggest such a mixture.

Katz relates to “lipo-derived stem cell[s]. . .[that are] substantially free of other cell types (e.g., adipocytes, red blood cells, other stromal cells, etc.) and extracellular matrix material.” (Katz, at Col. 2, lines 27-30). Further, Katz teaches that the stem cells are “preferably. . .completely free of such other cell types and matrix material” present in intact, non-disaggregated adipose tissue. (Katz, at Col. 2, lines 30-32). The stem cells described in Katz are obtained by processing adipose tissue to separate stem cells from the remainder of the cellular or extracellular material present in the (unprocessed) adipose tissue and the processing steps include washing and agitating adipose tissue to yield “lumps of various size” which are subsequently enzymatically or mechanically disaggregated. (Katz, at Col. 3, line 19 through Col. 4, line 6). As such, the adipose-derived stem cells in Katz are devoid of any unprocessed adipose tissue, including intact, non-disaggregated tissue fragments.

Similarly, Peterson does not teach or suggest a mixture of unprocessed, intact, non-disaggregated adipose tissue and a concentrated population of cells that comprise adipose-derived stem cells. Peterson describes the isolation of precursor cells from various tissues including blood, bone marrow, and adipose tissue. In the section entitled “Adipose Tissue as the Source of Precursor Cells”, Peterson describes “two embodiments” that relate to isolation of precursor cells from adipose tissue. (Peterson at Col. 9, lines 66-67). One embodiment involves isolation of precursor cells using affinity chromatography. Peterson teaches that the affinity binding method “requir[es] a step to produce a single-cell suspension before incubation with the antigen binding reagent.” (Peterson at Col. 10, lines 5-13, emphasis added). The other embodiment described in Peterson involves sedimentation. This embodiment also requires that the tissue is processed to produce a “single-cell suspension.” *Id.* at Col. 10, lines 17-20. Peterson teaches that single cell suspensions can be obtained by disaggregating the tissue enzymatically, e.g., with collagenase. Therefore, as with Katz, the compositions described in

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Peterson are not mixtures that contain “unprocessed adipose tissue comprising intact, non-disaggregated tissue fragments” as now recited in Applicants’ claims.

In sum, Applicants’ claims are directed to “compositions comprising a mixture of a first component that comprises unprocessed adipose tissue comprising intact non-disaggregated tissue fragments . . . mixed with a second component comprising a concentrated population of cells that comprises adipose-derived stem cells.” Neither Katz nor Peterson teaches or fairly suggests the claimed mixture. To the contrary, as discussed below, the teachings of Katz and Peterson lead the skilled artisan *away* from mixing adipose-derived stem cells with unprocessed adipose tissue. Furthermore, as discussed below, Applicants’ claimed mixture of a concentrated population of cells comprising adipose-derived stem cells and unprocessed adipose tissue has unexpected properties.

Katz and Peterson Teach Away from Applicants’ Invention

Katz describes the isolation and separation of lipo-derived stem cells from adipose tissue. Katz states that it is advantageous to separate the stem cells present in the intact adipose tissue from all other cells and extracellular matrix material present in intact adipose-tissue:

preferably, the stem cell is substantially free of other cell types (e.g. adipocytes, red blood cells, other stromal cells, etc.) and extracellular matrix material; more preferably, the stem cell is completely free of such other cell types and matrix material. (Katz, Col. 2, lines 27-32, emphasis added)

The skilled artisan, in view of the teachings of Katz, would not be led to combine adipose-derived stem cells with intact, non disaggregated adipose tissue, as Katz teaches that complete isolation of stem cells from other cellular or extracellular components present in intact, non-disaggregated adipose tissue, such as adipocytes, red blood cells, other stromal cells, and the like is preferred.

Peterson also teaches the desirability of completely isolating precursor cells from other components of adipose tissue. Specifically, Peterson teaches two embodiments that involve the use of adipose tissue as a source of precursor cells. Both embodiments require a step of disaggregating the tissue to achieve a single-cell suspension, which is then further processed to isolate the cells of interest. Peterson states that it is necessary to fully disaggregate and further process adipose tissue. (Peterson, Col. 10, lines 5-8, Col. 10, lines 15-20). Accordingly, the

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skilled artisan is led away from mixing adipose-derived stem cells with intact, non-disaggregated adipose tissue.

In sum, both Katz and Peterson teach away from Applicants' claimed invention as set forth in Claims 93-125, which supports Applicants' position that the claimed invention is not obvious.

Applicants' Invention Provides New and Unexpected Properties

Applicants' claimed mixtures provide for superior vascularity and tissue retention over compositions described in Katz and Peterson, which relate to isolated, or substantially isolated adipose-derived stem cells or precursor cells. Both Katz and Peterson describe seeding the isolated stem cells on various lattices, matrices, or scaffolds.

Briefly, Katz teaches that isolated stem cells can be seeded on biocompatible lattices, such as polymeric material including glycolic acid, lactic acid, propyl fumarate, etc., as well as matrigel. (*See*, Katz at Col. 10, line 27-Col. 11, line 36). Katz states:

Typically, the lattice is formed from polymeric material, having fibers as a mesh or sponge, typically with spaces on the order of between about 100 μm and about 300 μm . Such a structure provides sufficient area on which the cells can grow and proliferate. Desirably, the lattice is biodegradable over time, so that it will be absorbed into the animal matter as it develops. Suitable polymeric lattices, thus, can be formed from monomers such as glycolic acid, lactic acid, propyl fumarate, caprolactone, hyaluronan, hyaluronic acid, and the like. Other lattices can include proteins, polysaccharides, polyhydroxy acids, polyorthoesters, polyanhydrides, polyphosphazenes, or synthetic polymers (particularly biodegradable polymers)... Lattices suitable for inclusion into the composition can be derived from any suitable source (e.g., matrigel), and some commercial sources for suitable lattices exist (e.g., suitable of polyglycolic acid can be obtained from sources such as Ethicon, N.J.). Another suitable lattice can be derived from the acellular portion of adipose tissue--i.e., adipose tissue extracellular matrix matter substantially devoid of cells. (Katz at Col. 10, line 27-Col. 11, line 36, emphasis added)

Similarly, Peterson mentions that the isolated stem cells can be combined with a biocompatible carrier material or a prosthetic device. (*See*, Peterson at Col. 11, lines 29-52, Col. 12, lines 21-29). The carriers and prosthetic devices mentioned in Peterson, are, as with Katz, acellular.

Applicants submit herewith a Declaration of John Fraser, Ph.D., one of the named inventors on the instant application, and a specialist in the field of stem cell based therapies. Dr. Fraser states that implants comprising substantially isolated stem cells seeded on a lattice,

scaffold, or matrix such as the types mentioned in Katz and Peterson are reabsorbed over time, and/or do not have the characteristics of native soft tissue, and are thus not suitable for a large number of implants. (See, Fraser Decl., ¶¶ 5-7). Dr. Fraser's statements are supported by several articles published in peer-reviewed journals that detail the shortcomings and problems of using implants derived from isolated adipogenic cells seeded onto acellular lattices.

For example, studies have shown that cultured adipogenic cells seeded onto a polylactide support were able to generate adipose tissue, but that the amount of adipose cells peaked at two months, was substantially reduced (to approximately 40% of peak level) by three months, and was totally absent at all time points between five and twelve months post-implant. Other groups have reported similar results with transplants of preadipocytes on collagen sponges¹, hyaluronic scaffolds², and freeze-dried collagen³. (See also, Fraser Decl. at ¶7). Accordingly, the compositions taught in Katz and Peterson are not particularly useful for implantation, especially for breast reconstruction, breast augmentation and the repair of soft tissue defects. Fraser Decl. at ¶11.

By contrast, Applicants' claimed compositions provide unexpectedly improved properties. Example 1 of the specification illustrates the unexpected benefits of the claimed compositions, (*i.e.*, mixtures of processed lipoaspirate comprising a concentrated population of adipose-derived stem cells and unprocessed adipose tissue). Briefly, either adipose tissue alone, or adipose tissue mixed with a concentrated population of adipose-derived stem cells were implanted subcutaneously into the thigh or scalp of recipient rats. One month following implantation, histologic examination of the implants showed that the implants comprising a mixture of unprocessed and processed lipoaspirate improved the graft weight and vascularity compared to fat implants alone. (Specification at p. 40, lines 11-24, Fig. 5). These experimental results illustrate Applicants' surprising discovery that the claimed mixtures provide superior properties for tissue implantation. The unexpected benefits of the claimed mixtures could not have been predicted from the teachings of the cited art, which do not mention combining adipose-derived stem cells with unprocessed adipose tissue.

¹ Kimura, Y. et al. (2003) *Biomaterials* 24:2513-2521 (Annexed to Fraser Decl. as Exhibit B).

² Hemmrich, K. et al. (2005) *Biomaterials* 26:7025-7037 (Annexed to Fraser Decl. as Exhibit B).

³ Von Heimburg, D. et al. (2001) *Biomaterials* 22:429-438 (Annexed to Fraser Decl. as Exhibit B).

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Importantly, the surprising results described in Example 1 of the instant specification have been seen in humans. A clinical trial using Applicants methods and the results thereof are described in ¶¶14-19 of the Fraser Declaration. Briefly, adipose tissue was removed from women that had undergone surgery and radiation therapy for breast cancer. The adipose tissue was divided into two portions: the first portion of the adipose tissue was processed to isolate a concentrated cell population comprising adipose-derived stem cells; and the second portion was not processed. The first and second portions were mixed (to yield the presently claimed composition) and implanted into the breasts of the women. Tissue retention was measured at one month and at a final visit (mean, 11 months). The data show that there was no significant loss of benefit from 1 month to final measurement. Accordingly, Applicants' claimed compositions provide a breakthrough in the field of cosmetic and reconstructive surgery, in that the claimed mixtures exhibit volume retention over time and the characteristics of native soft tissue, factors not met by the compositions of Katz and Peterson.

In view of the evidence demonstrating that Applicants' claimed mixtures provide unexpected benefits over other implant material (e.g., the compositions described in Katz and Peterson), Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Applicants' Claimed Invention Satisfies a Long-Felt Unmet Need

Applicants invention satisfies, as of the filing date of the instant application, a long-felt unmet need for tissue implants that (1) are of a material that has the characteristics of native soft tissue (i.e.; it cannot be rigid); and (2) remain stable such that the reconstruction, repair or augmentation is retained over time.

As stated by Dr. Fraser, the field of cosmetic and reconstructive surgery widely recognized an unmet need for suitable tissue implants, (e.g., implants that (1) are of a material that has the characteristics of native soft tissue, and (2) remain stable over time), and that the methods available at the time were unsatisfactory. (Fraser Decl. at ¶5). The long-felt unmet need and failure of others are documented not only in several scientific journal articles published just prior to Applicants' effective filing date, but also from the continued recognition of the shortcomings of the commercially available methods for tissue implants. By way of example, von Heimburg *et al.* states “[c]urrently, there is no adequate implant material for the correction of

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soft tissue defects." (von Heimburg *et al.* (2001) *Biomaterials* 22:429-438, Abstract) (Annexed to Fraser Decl. as Exhibit B). von Heimburg *et al.* teaches that the available methods all show considerable disadvantages, including adverse reactions to synthetic materials, shrinkage of biologically-derived materials, and resorption and replacement of adipose tissue grafts with fibrous tissue. Likewise, Masuda *et al.* states that "[s]oft tissue augmentation is still an ongoing challenge in the field of plastic and reconstructive surgery... the available clinical approaches to overcoming these issues. . . [are all] associated with certain drawbacks." (Masuda *et al.* (2004) *Tissue Eng.* 10:523-535, 523) (Annexed to Fraser Decl. as Exhibit B). Patrick *et al.* note that "[t]he resorption of adipose tissue with extended periods is not a new problem ... Numerous strategies have been attempted to prevent adipose resorption following grafting." (Patrick *et al.* (2002) *Tissue Eng.* 8(2): 283-292, 292) (Annexed to Fraser Decl. as Exhibit B). Notably, the method described in Patrick *et al.* was unsuccessful. Stosich *et al.* reiterate this point, stating "[s]oft tissue reconstruction or augmentation represents one of the most acute challenges in all surgical procedures". (Stosich *et al.* (2007) *Plast. Reconst. Surg.* 119:71-83) (Annexed to Fraser Decl. as Exhibit B). Stosich enumerates the various drawbacks of implants comprising autologous soft tissue, synthetic implants, and various matrices seeded with isolated stem cells. (Stosich *et al.* at 72). Although each of these studies discusses the need for stable tissue implants, none of these studies describe a composition that possesses the characteristics required for soft tissue defect repair described above. (See, e.g., von Heimburg *et al.*, Masuda *et al.*, Stosich *et al.*, Fraser Decl., and references cited therein).

As demonstrated in Applicants' pre-clinical results and the clinical results described above, Applicants' invention satisfies this unmet need in the field because for the first time, characteristics of native soft tissue and long-term retention by the body have been provided. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

As set forth above, Applicants' have demonstrated that the Katz and Peterson references are insufficient to support a *prima facie* case of obviousness under 35 U.S.C. § 103(a) because the references not only fail to teach or suggest each element of the claims, but in fact teach away from Applicants' claimed invention. Furthermore, *even if* the Examiner finds that the Katz and Peterson references support a *prima facie* case, Applicants have demonstrated that the claimed

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compositions provide unexpected benefits over prior art compositions, and that because of this unexpected benefit, Applicants were able to satisfy a long-felt unmet need in the field. That is, Applicants present a nexus between the unexpected benefits provided by the claimed compositions and the long felt unmet need satisfied, which provides strong evidence of non-obviousness. Accordingly, in view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

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CONCLUSION

In view of the above amendments and remarks, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: April 9, 2008

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